UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/588,754	02/02/2007	Jalaj Arora	5999-0525PUS3	2942

54080 7590 04/01/2010

BIRCH, STEWART, KOLASCH & BIRCH, LLP
P.O. BOX 747
FALLS CHURCH, VA 22040-0747

EXAMINER	
COUGHLIN, MATTHEW P	
ART UNIT	PAPER NUMBER
1626	

MAIL DATE	DELIVERY MODE
04/01/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/588,754	ARORA ET AL.	
	Examiner	Art Unit	
	Matthew P. Coughlin	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 January 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28 and 30-38* is/are pending in the application.

4a) Of the above claim(s) *4,20 and 32-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 5-19,21-28,30 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *06/08/2007, 02/02/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-28 and 30-38 are pending in the application. Claims 1-3, 5-19, 21-28 and 30-31 are rejected. Claims 4, 20 and 32-38 are withdrawn from further consideration.

Priority

The contents of Provisional No. 60/545292 were reviewed due to the presence of intervening prior art. No support could be found for species of the elected Group III. The priority date for the instant claims is therefore February 17th, 2005.

Election/Restrictions

Applicant's election with traverse of the species:

3-(5-(2-(5-(3-chloro-phenyl)-isoxazol-3-yl)-pyrrolidin-1-yl)-4-methyl-4H-[1,2,4]triazol-3-yl)-pyridine

to prosecute the invention of Group III in the reply filed on January 15th, 2010 is acknowledged. The traversal is on the ground(s) that there is no undue burden. This is not found persuasive because the different core heterocycles of Groups I-VI cause the Groups to be classified in separate classes and subclasses, which represents a serious burden for search. Furthermore, the Examiner must perform a commercial database search for each inventive group which further represents a serious burden. In addition, there is no patentable co-action between the compound and method groups and a reference anticipating one member will not render another obvious. Each group is directed to art recognized divergent subject matter which require different searching strategies for each group. Moreover, the examiner must perform a commercial database search on the subject matter of each group in addition to a paper search, which is quite burdensome to the examiner.

The seven-way restriction requirement between Groups I-VII is still deemed proper and is therefore made FINAL.

Applicant's traversal with respect to the election of species has been found persuasive since the entire scope of Group III has been searched. Therefore, the election of species has been withdrawn.

In the office action dated September 4th, 2009, the Examiner stated that Groups I-VI were drawn to claims 1-28 and 30-30. The claims listed should have been 1-28 and 30-31 (in part).

Claims 4, 20 and 32-38 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on January 15th, 2010.

Information Disclosure Statement

The Examiner has considered the Information Disclosure Statement(s) filed on June 8th, 2007 and February 2nd, 2007.

Specification

The disclosure is objected to because of the following informalities: Page 22 of the specification appears to contain a few misplaced paragraphs:

$_6$alkyl$(SO_2)R^5$, C_{0-6}alkyl$(SO)R^5$, OC_{2-6}alkyl$(SO)R^5$ and a 5- or 6-membered ring containing atoms independently selected from the group consisting of C, N, O and S;

R^5 and R^6 are independently selected from, H, C_{1-6}alkyl, C_{3-7}cycloalkyl and aryl;

m is selected from 0, 1, 2, 3 or 4;
n is selected from 0, 1, 2, 3 or 4;
p is selected from 0, 1, 2, 3 or 4; and
a salt or hydrate thereof.

Appropriate correction is required.

Claim Objections

Claims 1, 2 and 24 do not end in periods.

Claim 27 should be amended to separate each of the species by commas.

Claim Rejections - 35 USC § 112 - 2md paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3, 5-19, 21-26, 28 and 30-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation that R4 can be:

C_{1-6}alkyl$(SO)C_{0-6}$alkyl, C_{1-6}alkyl$(SO_2)C_{0-6}$alkyl, $(SO)C_{0-6}$alkyl, $(SO_2)C_{0-6}$alkyl,

The structure of the above groups is unclear where the alkyl group is C_0. Such groups appear to have an improper valence. The same issue exists for the definitions of R2 and R3 where they are:

$C_{0-4}alkyl(S)C_{0-4}alkyl$, $C_{1-4}alkyl(SO)C_{0-4}alkyl$, $C_{1-4}alkyl(SO_2)C_{0-4}alkyl$, $(SO)C_{0-4}alkyl$, $(SO_2)C_{0-4}alkyl$.

Claim Rejections - 35 USC § 112 - 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5-19, 21-28 and 30-31 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for compound of formula I or a pharmaceutically acceptable salt thereof, does not reasonably provide enablement for non-pharmaceutically acceptable salts of a compound of formula I. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is *undue*. These factors include, but are not limited to: (a) breadth of the claims; (b) nature of the invention; (c) state of the prior art; (d) level of one of ordinary skill in the art; (e) level of predictability in the art; (f) amount of direction provided by the inventor; (g) existence of working examples; and (h) quantity of experimentation needed to make or use the invention based on the content of the disclosure. (See *Ex parte Forman* 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and *In re Wands*, 8 USPQ2d 1400 (Fed.

Cir. 1988).

The above factors, regarding the present invention, are summarized as follows:

(a) *Breadth of the claims* - The breadth of the claims includes all the possible compounds of formula I as well as all possible salts thereof, including pharmaceutically acceptable salts and non-pharmaceutically acceptable salts thereof.

(b) *Nature of the invention* - The nature of the invention is drawn to compounds and salts thereof that have utility, according to Applicant's specification, in the pharmaceutical treatment of diseases including Alzheimer's disease.

(c) *State of the prior art* - The state of the prior art with respect to the generation of pharmaceutically acceptable salts has advanced such that a person having ordinary skill in the art is able to generate pharmaceutically acceptable salts wherein the choice of an acid or base used to generate said salt (i.e. a salt-former) is chosen from a sub-set of particularly well-known and commonly utilized acids or bases. The Federal Circuit (*Pfizer, Inc. v. Apotex, Inc*., 480 F.3d 1348, 82 USPQ2d 1321) has established that the generation of pharmaceutically acceptable salts by a person having ordinary skill in the art can proceed with a reasonable expectation of success and without undue experimentation since the group of potential pharmaceutically acceptable salt-formers known to those of ordinary skill in the art is relatively small. See also MPEP 2143, Section E. A person having ordinary skill in the art is able to recognize pharmaceutically acceptable salt-formers since the class of pharmaceutically acceptable salt-formers is well known. See, for instance, Berge et al. J. Pharm. Sci. 1977, 66, 1-19.

On the other hand, the group of potential salt-formers that are non-pharmaceutically acceptable is exceedingly vast. Beyond the scope of pharmaceutically acceptable salt-formers, a person having ordinary skill in the art cannot readily envision non-pharmaceutically acceptable salt-formers that would be reasonably expected to be useful in a pharmaceutical setting. There is no teaching in the prior art that enables a person having ordinary skill in the art to navigate the diverse non-pharmaceutically acceptable salt-formers when attempting to develop salts useful in a pharmaceutical setting particularly because such non-pharmaceutically acceptable salt-formers have yet to be extensively studied in a pharmaceutical context.

(d) *Level of one of ordinary skill in the art* - The artisans synthesizing applicant's salts, would be a collaborative team of synthetic chemists and/or health practitioners, possessing commensurate degree level and/or skill in the art, as well as several years of professional experience. Said artisans would be familiar with the process of generating pharmaceutically acceptable salts by choosing from a sub-set of known pharmaceutically

acceptable salt-formers and generating pharmaceutically acceptable salts of candidate drug compounds. The process of choosing from the exceedingly vast array of non-pharmaceutically acceptable salt-formers when developing and testing salts of drug candidates is not within the grasp of one of ordinary skill in the art absent undue experimentation. A person having ordinary skill in the art does not possess the ability to predict, a priori, which salt-formers outside of pharmaceutically acceptable salt-formers can be reasonably expected to be useful in a pharmaceutical setting.

(e) *Level of predictability in the art* – The properties of a salt are unpredictable if given only the properties of the parent compound. For instance, Berge et al. teach (page 2):

> *Various salts of the same compound often behave quite differently because of the physical, chemical, and thermodynamic properties they impart to the parent compound. For example, a salt's hydrophobicity and high crystal lattice energy can affect dissolution rate and, hence, bioavailability.*

Even in the face of teachings that salts can have unpredictable properties, the Federal Circuit (*Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 82 USPQ2d 1321) still maintained that the generation of a group of pharmaceutically acceptable salts is within routine experimentation of a person having ordinary skill in the art since there is a reasonable, albeit non-absolute, expectation of success in making and using said pharmaceutically acceptable salts. The courts have not established whether this rationale applies to all types of salts; however, the next two paragraphs discuss the merits of such a possible generalization.

Various salt-formers are known; however, only a small sub-set has been studied in the context of pharmaceutical applications. These well studied salt-formers belong to the class known as pharmaceutically acceptable salt-formers since the drugs generated after salt formation have been tested *in vitro* and *in vivo* and have been demonstrated to possess benefits with respect to the pharmaceutical safety and utility. The reasonable expectation of success in investigating pharmaceutically acceptable salts is based on a posteriori knowledge from previous studies which have demonstrated the safety and usefulness of particular pharmaceutically acceptable salt-formers.

There is extremely low predictability in selecting a particular non-pharmaceutically acceptable salt-former out of the vast array of possible choices and determining whether products generated from salt formation will be safe and/or effective in a pharmaceutical setting. There is a significant degree of unpredictability in the properties of particular salts of a given compound and in the absence of data from other pharmaceutical applications that have clearly demonstrated whether particular salt-formers can be reasonable expected to provide salts with safe and effective pharmaceutical utility, a person having ordinary skill cannot reasonably predict whether particular salt-formers should or should not be investigated.

(f) *Amount of direction provided by the inventor* - The application, together with the prior art, provides sufficient guidance to a person having ordinary skill in the art in order to generate pharmaceutically acceptable salts.

There is no guidance in the instant specification that would enable a person having ordinary skill in the art to select appropriate non-pharmaceutically acceptable salts for use in the instant utility. The instant scope is likely inclusive of inoperative embodiments since it is extremely unlikely that each and every non-pharmaceutically acceptable salt will have pharmaceutical utility. MPEP 2164.08(b) states:

> *The presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. […]*
>
> *[C]laims reading on significant numbers of inoperative embodiments would render claims nonenabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative. Atlas Powder Co. v. E.I. duPont de Nemours & Co., 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984); In re Cook, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971)*

In the instance case, the specification provides no guidance in using non-pharmaceutically acceptable salt-formers in order to generate salts. As noted in section (e), neither the instant specification nor the prior art provides guidance as to which non-pharmaceutically acceptable salts are likely to be inoperative.

(g) *Existence of working examples* - Applicant lacks working examples of any salts, let alone, a significant number of salts that would reasonably assure a person having ordinary skill in the art that the entire scope of both pharmaceutically and non-pharmaceutically acceptable salts will have the instant utility.

(h) *Quantity of experimentation needed to make or use the invention based on the content of the disclosure* - As noted in section (e), a person having ordinary skill in the art is readily able to generate pharmaceutically acceptable salts with a reasonable expectation of success and undue experimentation. The reason is that the pharmaceutical field has been studying the use of particular salt-formers extensively with various types of compounds in various pharmaceutical contexts. These well-studied salt-formers have become known to a person having ordinary skill in the art as pharmaceutically acceptable salt formers and have been demonstrated to be safe and effective in pharmaceutical uses. On the other hand, non-pharmaceutically acceptable salt-formers have not been

> extensively studied and there are no general teachings in the art that would lead a person having ordinary skill in the art to be able to choose from the vast number of non-pharmaceutically acceptable salt-formers in order to generate salts useful in the instant utility. Rather, a person having ordinary skill in the art, in order to make and use the full scope of the instant scope, must perform extensive studies on potential drugs made using salt-formers that have yet to be properly examined for use in pharmaceutical applications. The studies include *in vivo* toxicity studies, *in vitro* and *in vivo* efficacy studies, physical property studies including polymorphism, etc. Instead of relying on a large base of knowledge known in the art that exists for generating pharmaceutically acceptable salts, a person having ordinary skill in the art must generate such knowledge on his or her own for each potential non-pharmaceutically acceptable salt-former and is therefore faced with undue experimentation in order to make and use the full scope of non-pharmaceutically acceptable salts.

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. {*In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)}.

The determination that *undue experimentation* would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations. (*In re Wands,* 858 F.2d at 737, 8 USPQ2d at 1404). These factual considerations are discussed comprehensively in MPEP § 2164.08 (scope or breadth of the claims), § 2164.05(a) (nature of the invention and state of the prior art), § 2164.05(b) (level of one of ordinary skill), § 2164.03 (level of predictability in the art and amount of direction provided by the inventor), § 2164.02 (the existence of working examples) and § 2164.06 (quantity of experimentation needed to make or use the invention based on the content of the disclosure).

Based on a preponderance of the evidence presented herein, the

conclusion that applicant is insufficiently enabled for making and using non-pharmaceutically acceptable salts of compounds of formula I, is clearly justified.

Claims 1-3, 5-19, 21-28 and 30-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a compound of formula I or a pharmaceutically acceptable salt thereof, does not reasonably provide enablement for a hydrate of a compound of formula I. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is *undue*. These factors include, but are not limited to: (a) breadth of the claims; (b) nature of the invention; (c) state of the prior art; (d) level of one of ordinary skill in the art; (e) level of predictability in the art; (f) amount of direction provided by the inventor; (g) existence of working examples; and (h) quantity of experimentation needed to make or use the invention based on the content of the disclosure. (See *Ex parte Forman* 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

The above factors, regarding the present invention, are summarized as follows:

(a) *Breadth of the claims* - The breadth of the claims includes all of the tens of thousands of compounds of formula I as well as presently unknown compounds embraced by the term hydrates.

(b) *Nature of the invention* - The nature of the invention is drawn to the chemical synthesis of hydrates and pharmaceutical compositions thereof.

(c) *State of the prior art* - The state of the art recognizes that the formation, composition and therapeutic activity of hydrates is unpredictable. The Federal Circuit (in *SmithKline Beecham Corp. v. Apotex Corp.*, 74 USPQ2d 1398, 1409 (Fed.Cir. 2005)) has recognized solvates and hydrates, i.e. solvates where the solvent is water, as examples of polymorphs or pseudopolymorphs:

> *"Polymorphs" are distinct crystalline structures containing the same molecules. These structural differences can affect various properties of the crystals, such as melting points and hardness (e.g., graphite and diamonds are both crystalline forms of carbon) .... [P]seudopolymorphs are often loosely called polymorphs ... Pseudopolymorphs not only have their molecules arranged differently but also have a slightly different molecular composition. A common type of pseudopolymorph is a solvate, which is a crystal in which the molecules defining the crystal structure "trap" molecules of a solvent. The crystal molecules and the solvent molecules then bond to form an altered crystalline structure.*

While the Federal Circuit addresses the fact that particular physical properties of hydrates can be different from the parent compound, the state of the prior art also recognizes that pharmaceutical properties, such as dissolution (which affects a particular compound's ability to elicit a desired biological response), can also be significantly different in hydrates compared to the parent compound. Giron (*J. Therm. Anal. Cal.* **2001**, *64*, page 39, internal citations omitted) teaches that:

> *The effect of polymorphism on bioavailability or toxicity is the most important consequence for drug substances if the bioavailability is mediated via dissolution. For the most famous case of chloroamphenicol palmitate, the active polymorph is not the thermodynamical [sic] stable one.*

Similarly, Souillac, et al., Characterization of Delivery Systems, Differential Scanning Calorimetry, pages 217-218 (in Encyclopedia of Controlled Drug Delivery, 1999, John Wiley & Sons, pages 212-227), teach that different polymorphs of the same drug can have different therapeutic activity:

> *Because different polymorphic forms of the same drug exhibit significant differences in their physical characteristics, therapeutic activity from one form to another may be different. Studying the polymorphism of a drug and the relative stability of the different polymorphs is a critical part of pre-formulation development.*

With respect to Applicant's claim to pharmaceutical compositions containing hydrates, the state of the art with respect to the generation of formulations containing crystalline forms is complex. The preparation of pharmaceutical formulations can require milling, adding excipients, surfactants, etc. Giron (*J. Therm. Anal. Cal.* **2002**, *68*, page 342) teaches that:

> *The formation of solvates or hydrates followed by drying into an anhydrous form can be extremely critical for the drying upscale if several hydrates, several anhydrous forms and the amorphous state may occur. Furthermore, the drug substance may undergo transformation during milling. For the dosage form, solvate or hydrate formation may occur during granulation. Excipients may accelerate transformation changes during mixing, tabletting. From our experience these highly critical questions have to be addressed and resolved before the transfer from development to production.*

(d) *Level of one of ordinary skill in the art* - The artisans synthesizing Applicant's hydrates and pharmaceutical compositions thereof, would be a collaborative team of synthetic chemists and/or health practitioners, possessing commensurate degree level (at least a B.S. degree) and/or skill in the art, as well as several years of professional experience.

(e) *Level of predictability in the art* - As mentioned in section (c), there is a large degree of uncertainty in predicting the properties of a hydrate given only the properties of the parent compound. There is no predictability in determining that a hydrate will possess the same beneficial properties that make a given compound a drug candidate or similarly that a hydrate will not possess the undesired properties that make a given compound unsuitable for pharmaceutical use.

More importantly, there is a severe lack of predictability in determining whether a given compound will even form a hydrate and, if so, whether multiple polymorphic forms can exist. B. Rodriquez-Spong et al. (*Advanced Drug Delivery Reviews*, **2004**, *56*, page 263) teach that:

> *In general, scientists have yet to achieve a satisfactory degree of control over polymorphism and in particular there is no method to guarantee the production of even the most thermodynamically stable form of a compound. More problematic, and a commonly encountered task for pharmaceutical companies, is finding all forms of a compound that can exist under ambient conditions.*

(f) *Amount of direction provided by the inventor* - The application is negligent regarding direction with respect to making and using hydrates. The specification merely mentions the Applicant's intention to make hydrates, without teaching the preparation thereof.

(g) *Existence of working examples* - While the claims recite hydrates, no working examples show their formation. As stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190, 1194 (Fed. Cir. 1993):

> *The specification purports to teach, with over fifty examples, the preparation of the claimed compounds ... However ... there is no evidence that such compounds exist ... [T]he examples ... do not produce the postulated compounds ... [T]here is ... no evidence that such compounds even exist.*

The specification shows no evidence of the formation and actual existence of hydrates. Hence, Applicant must show formation of hydrates or limit the claims accordingly.

(h) *Quantity of experimentation needed to make or use the invention based on the content of the disclosure* - Given the state of the art and lack of predictability discussed in sections (c) and (e), undue experimentation is needed to practice the full scope of Applicant's instant invention especially in view of the lack of direction discussed in sections (f) and (g). Giron (*J. Therm. Anal.* Cal. 2002, *68*, page 344) teaches that a study of hydrates requires a full research program and is well beyond that of routine experimentation:

> *The most challenging issue in the pharmaceutical industry is the proper study and characterization of polymorphs, and solvates [...]. Studies including crystallizations, equilibrations, granulating, tabletting have to be conducted in order to detect polymorphs and to characterize them. If properties (solubilities, dissolution, stability, and performance) are different, the impact on the dosage form has to be studied. Depending on the outcome, quantitative validated methods have to be developed and specification set for drug substance or for excipient or/and for the dosage form. Since changes may occur during processing or storage under the influence of mechanic stress, temperature, pressure and moisture, a proper study design has to be set and adequate methods have to be used.*

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. {*In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513

(Fed. Cir. 1993)}.

The determination that *undue experimentation* would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations. (*In re Wands,* 858 F.2d at 737, 8 USPQ2d at 1404). These factual considerations are discussed comprehensively in MPEP § 2164.08 (scope or breadth of the claims), § 2164.05(a) (nature of the invention and state of the prior art), § 2164.05(b) (level of one of ordinary skill), § 2164.03 (level of predictability in the art and amount of direction provided by the inventor), § 2164.02 (the existence of working examples) and § 2164.06 (quantity of experimentation needed to make or use the invention based on the content of the disclosure).

Based on a preponderance of the evidence presented herein, the conclusion that applicant is insufficiently enabled for making and using hydrates of compounds of formula I as well as pharmaceutical compositions containing a hydrate of a compound formula I, is clearly justified.

Claims 28 and 30-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

(1) a compound of formula I, and

(2) a pharmaceutical composition thereof comprising a therapeutically effective, but not preventatively effective, amount of a compound of formula I,

does not reasonably provide enablement for:

(1) a pharmaceutical composition comprising a preventatively effective amount of a compound of formula I,

(2) a compound of formula I for use in therapy, or

(3) a compound of formula I for use in the treatment or prevention of mGluR 5 mediated disorders.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is *undue*. These factors include, but are not limited to: (a) breadth of the claims; (b) nature of the invention; (c) state of the prior art; (d) level of one of ordinary skill in the art; (e) level of predictability in the art; (f) amount of direction provided by the inventor; (g) existence of working examples; and (h) quantity of experimentation needed to make or use the invention based on the content of the disclosure. (See *Ex parte Forman* 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

The above factors, regarding the present invention, are summarized as follows:

(a) ***Breadth of the claims*** - The breadth of the claims is drawn to all compounds of formula I and pharmaceutical compositions thereof with intended uses for prevention and treatment of various disorders. NOTE: "Treatment" and "therapeutically" are defined as including prevention on page 23, lines 20-23 of the specification.

The diseases, disorders, or conditions encompassed by the instant claims include, for example, Alzheimer's disease, pain, stroke, etc.

(b) ***Nature of the invention*** - The nature of the invention is drawn to a compounds and compositions thereof for use in the pharmaceutical treatment and prevention of diseases and disorders.

(c,e) ***State of the prior art* and predictability in the art** - The state of the prior art is that the pharmacological art involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat which specific disease by what mechanism). There is no absolute

predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

According to the specification, the instant compounds are antagonists for mGluR 5; however, the prior art has not advanced to the point where a demonstration of activity at mGluR 5 can be extrapolated to the treatment or prevention of "mGluR 5 mediated disorders." There is no teaching the prior art that enables a person having ordinary skill in the art to recognize which diseases or disorders fall within the scope of "mGluR 5 mediates disorders" and would be treatable or preventable using the instant compounds. Bird et al. (Trends in Pharmaceutical Sciences, 30, 2009, 617-623) teach that the mGlu5 receptor is involved in many different pathways and modulating of mGlu5 function will likely affect multiple pathways (page 618). There is no predictability in the art as to how a particular mGlu5 binder will elicit a given response or what that response may be. Instead, the ability to treat or prevent a disease that acts through the mGlu5 receptor requires in depth studies to study the effect of the treatments on the desired pathways and other distinct pathways.

Furthermore, claim 30 is drawn to therapy, in general, and includes the treatment and prevention of various diseases and disorders including cancer. The state of the art with respect to cancer is that despite the common result of uncontrolled cell growth and replication, the various types of cancers have widely varied causes. Luo et al. (Cell, 2009, 136, pages 823-837) teach that (p. 823):

> *[I]t is clear that there is tremendous complexity and heterogeneity in the patterns of mutations in tumors of different origins.*

Accordingly, despite the common phenotypic traits of tumors brought upon by genetic alterations, the underlying causes result in a significant complexity in treating cancer generally. There is no known target that can be activated/inhibited that would be expected to result in the treatment of all types of cancer generally. Furthermore, despite that particular therapies, such as, radiation and chemotherapy, are used for a variety of cancers, these therapies are still not fully understood. Luo et al. teach that (p. 824):

> *[W]e still do not have a clear molecular understanding of why these agents work to selectively kill tumor cells and, conversely, why they eventually fail.*

Therefore, any claim to the treatment of cancer, in general, requires the support of extensive studies to demonstrate that the particular mode of treatment applies to treating all types of cancer since there is no mode of action that can reliably lead to the treatment of all types of cancer.

(d) ***Level of one of ordinary skill in the art*** - The artisans making and using applicant's pharmaceutical compositions would be a

collaborative team of synthetic chemists and/or health practitioners, possessing commensurate degree level and/or skill in the art, as well as several years of professional experience. The level of skill in the art is high; however, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by *in vitro* or *in vivo* screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

(f-g) ***Amount of direction provided by the inventor and existence of working examples*** - The only direction or guidance present in the instant specification is the list of diseases and disorders on pages 2-4 of the specification that may be treatable using the instant compounds. There are no working examples present for the treatment or prevention of any disease or disorder by administering the instant compounds.

Test assays and procedures are provided in the specification on pages 81-83 for measuring Group I receptor antagonist activity; however, the disclosure does not provide how the *in vitro* data system correlates to the treatment of the assorted disorders of the instant claims.

Applicant has provided an *in vivo* assay on pages 83-85, which appears to be predictive of the ability to treat, but not prevent, gastro-esophageal reflux disease; however, no data has been presented for this assay and it is not clear if the instant compounds have been studied in this assay.

With respect to Applicant's claim to prevention, there is no evidence of record, which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the numerous diseases/disorders or conditions claimed herein. That a single compound can be used to treat or prevent all diseases/disorders and conditions embraced by the claim is an incredible finding for which Applicant has not provided supporting evidence. Applicant has not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for treating or preventing any or all of the diseases/disorders or conditions by administering the instant claimed compound.

Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved." See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(h) ***Quantity of experimentation needed to make or use the invention based on the content of the disclosure*** - The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine what diseases, disorders, or conditions out of all diseases, disorders, or conditions would be benefited by a compound of formula I and would furthermore then have to determine which of the claimed compounds in the instant invention would provide treatment or prevention of the diseases.

With particular respect to the treatment any type of cancer,

as instantly claimed, an undue amount of experimentation is required. Luo et al. teach that the majority of cancer therapies fail when applied generally in that (p. 833):

> *It is very likely that the oncogenes and non-oncogenes to which tumors are addicted will serve as the targets of successful cancer therapies in the future. However, it is already clear that each of even the best therapies applied alone eventually fail in the majority of cases.*

Therefore, the sum of the entire efforts in the field of cancer research has resulted in treatment methods that are not broadly applicable; however, Applicant claims that the instant compounds are the first and only broadly applicable cancer treatment despite the fact that Applicant has merely shown activity in assays where other prior compounds have shown activity and then failed to provide a broad treatment ability.

In fact, Luo et al. teach that even the best individual therapies can only be considered as filters to remove particular subsets of cancer cells with particular properties. Therefore, the most likely broadly applicable cancer treatment will be through a series of treatments with differing targets. Applicant has not provided sufficient teaching in the instant specification to allow a person of ordinary skill in the art to treat all types of cancer using either the instant compounds alone or in an orthogonal therapy approach. Rather, in order to practice the full scope the instant invention, a person of ordinary skill in the art would need to develop a treatment method that has eluded the entire field of cancer research.

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. {*In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)}.

The specification fails to provide sufficient support of the broad use of compositions containing the claimed compounds in the treatment, of a disease or a disorder or a condition responsive to inhibiting dopamine reuptake. As a result necessitating one of skill to perform an exhaustive search for which diseases can be treated by what compounds of the invention in order to practice the claimed invention.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which diseases can be treated by the compound encompassed in the instant claims, with no assurance of success.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

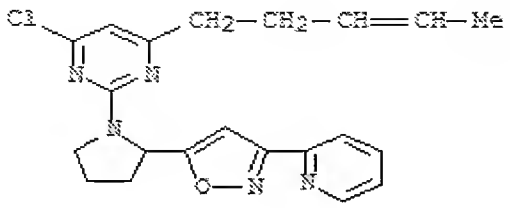
> A person shall be entitled to a patent unless -
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 3, 5, 9, 10, 11, 12, 13, 17, 18, 19, 21, 22, 26, 28 and 30 rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 7,579,349 by Nowak et al.

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the

reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Nowak et al. teach the following species in Example 43 as a solution:



.

Applicant is further directed to CAS Registry No's. 851435-10-4, 851435-09-1, 851435-08-0, 851435-07-9, 851435-06-8, 851435-05-7, 851435-04-6, 851435-02-4, 851434-92-9, 851434-91-8 and 851435-40-0P, which each anticipate the instant claims and are reported by Nowak et al.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Matthew P. Coughlin whose telephone number is (571)270-1311. The examiner can normally be reached on Monday through Thursday from 7:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on 571-272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Matthew P. Coughlin/ /Rebecca L Anderson/
Examiner, Art Unit 1626 Primary Examiner, Art Unit 1626